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14. ABSTRACT
We found that the direct image based and contour based alignment methods are both reliable to detect translational setup errors for patients with prostate cancer. In the longitudinal direction, the measurement uncertainties are slightly increased with the direct image alignment method when compared to the contour alignment method. Since the manual adjustments are necessary with the both alignment methods, the results of this study may subject to inter-observer variations. Further study will investigate the effect of inter-observer variations between the two methods. With a proof of principle study, we found that the multiple adaptive plan (MAP) approach is a clinically feasible strategy. Verification plans calculated with daily MV-CBCT can further provide patient specific dose guidance.

15. SUBJECT TERMS
Adaptive Radiotherapy, Image guided Radiotherapy, Prostate cancer, Pelvic Lymph nodes

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Introduction

It is estimated that 40% or more of patients with intermediate to high risk prostate cancer will relapse locally and systemically within five years after definitive radiotherapy. We hypothesize that this high rate of failure is partly due to under-irradiation of the pelvic lymph nodes. One of the challenges to using IMRT in concurrent treatment of the prostate and the pelvic lymph nodes is the independent movement of the prostate relative to the lymph nodes, rendering the conventional iso-center shifting method of tracking prostate movement inadequate. The purpose of this research is to develop a novel method using multi-adaptive plan (MAP) IMRT to accommodate independent movement of the two targeted tumor volumes. In order to evaluate effectiveness of the MAP IMRT approach, we first establish a baseline benchmark by creating a set of ideal IMRT plans for each patient based on the daily acquired mega-voltage cone beam CT, which represents the ideal case of daily online treatment planning. Based on this established benchmark, we can further evaluate two adaptive strategies: strategy A creates a set of IMRT plans individually optimizing on a series of possible prostate positions in the planning CT; and strategy B creates a set of multi-adaptive plans by dynamically adjusting the radiation apertures to accommodate the daily position of the prostate.

Body

(a) Obtain IRB approvals

During this initial period of research, the PI and her co-investigators spent about 6 months to establish protocols involving human subjects. Immediately after the notification of the DOD award, the PI submitted (dated on December 3, 2007) the first version of application of involving human research subjects to the Institution of Review Board (IRB) of the University of California at San Francisco (UCSF), referred to as the Committee on Human Research (CHR). This first application was approved by CHR of UCSF on March 5, 2008. In order to compliance with the guideline of DOD on research involving human subjects, the first version of the IRB application was modified to include patient's consent for the use of their treatment data for this research project. The modified IRB application was sent to the Office of Research Protections (ORP) and Human Research Protection Office (HRPO) at the United States Army Medical Research and Materiel Command (USAMRMC) for initial review and subsequently sent to CHR of UCSF for approval. The UCSF CHR approved the second application on August 5, 2008. Upon careful review by the specialist at OPR and HRPO of USAMRMC, further modification of the IRB was suggested. The final IRB application was approved by CHR of UCSF on October 29, 2008, and was subsequently approved on November 17, 2008 by the ORP and HRPO Office at USAMRMC.

According to the patient selection criteria outlined on the approved IRB application, fifty patients were contacted to consent for using their treatment data for this research project. As of March 30, 2009, sixteen patients agreed to participate in this research project and ten patients were randomly selected for the study.

(b) Assess accuracy of image registration methods

After IBR approval and obtaining the consents from patients who agreed to participate in the study, we immediately proceeded to conduct the task 1 item (2) as outline in the Statement of Work (SOW) to assess accuracy of image registration methods. The abstract of this work has

been accepted and will be presented in the annual meeting of American Association of Physicists in Medicine (AAPM) on July 26, 2009.

As stated in the statement of work (SOW), our initial plan was to compare three different image registration algorithms utilized in three different commercial systems to determine accuracy of my ability to detect the patient setup error and then subsequently to determine the prostate motion relative to the pelvic bone. Among these three systems, we recognized that the image management system used in our clinical practice (Oncology Workstation, Siemens Medical Solution) only detected the translational shifts and omitted the rotational shifts. The Pinnacle treatment planning system (Philips Medical Systems) provided an option of either including or excluding rotational shifts. The Corvus treatment planning system (North American Scientific Corp.) utilized both translation and rotation shifts. In order to validate clinical data of patient setup errors obtained in the Siemens Oncology Workstation, we decided to focus on translation shifts. Therefore, the Corvus treatment planning system is not used. Furthermore, with the conventional treatment couch, only translational shifts can be compensated by moving the treatment couch or shifting MLC leaves as we proposed in an algorithm developed in our group (1).

Although both systems (Siemens Oncology Workstation and Pinnacle treatment planning system) equipped with automatic image registration tools based on the mutual information metrics, we found that these automatic tools still require somewhat human intervention (or manual adjustment). The question is how to objectively evaluate the result of image registration. Visual inspection is a commonly used method to access the image registration results based on the overlap of the bony structures. Because of different image contrasts between the planning CT and the verification MV-CBCT, it is rather difficult to detect a small discrepancy by visually inspecting alignment of bony structures with the planning CT superimposed on the MV-CBCT. This method is referred to as the direct image alignment method. Instead of superimposing two image sets together, which substantially burred the image edges, we superimposed the contours of bony structures from the planning CT to the images of the verification MV-CBCT (or visa versa), aligning the contours of the bony structures to the corresponding bony structures in the verification images. This method is referred to as the contour alignment method. Figure 1 illustrated the direct image alignment method and the contour alignment method.

(a) Direct Image Alignment (b) Contour Based Alignment

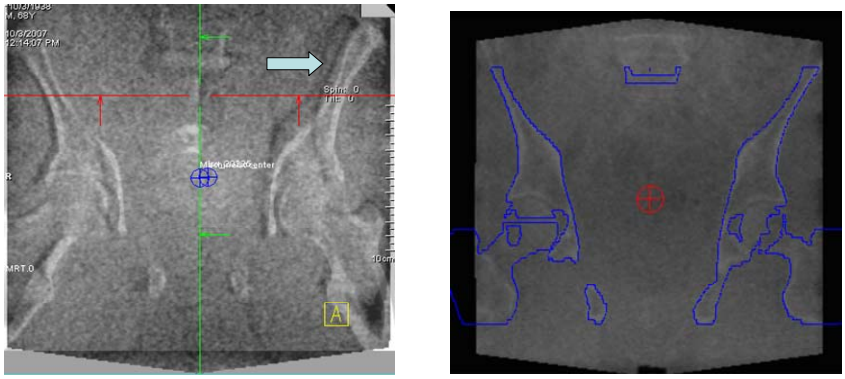

Figure1. (a) The planning CT (bone appeared in white) is superimposed in the MV-CBCT (bone appeared in bark). The arrow pointed the mis-alignment in the region. (b) The contour of the pelvic bone (in blue lines) is superimposed in the MV-CBCT (bone appears in gray).

For Ten patients with high-risk prostate cancer, who were underwent concurrent treatment of the pelvic lymph nodes and prostate in our clinic, were randomly selected for this study. For each patient, an extended field of view (FOV) MVCBCT was taken on the first day, and 8 patients received the reduced FOV – MVCBCT on the subsequent treatments. We performed all image registration in a commercially available treatment planning system (Pinnacle 8.0, Philips Medical Systems, Milpitas, CA). In order to perform the contour image registration, the pelvic bone contour was created on the planning CT slices by the auto-contouring tool in the planning software. The MVCBCT was transferred to the Pinnacle treatment planning system via DICOM format and manually registered with the planning CT based on the direct image alignment and the contour alignment methods. The translational shifts of both methods were recorded for data analysis. For each patient, each alignment method was repeated three times in three different days by one observer.

For each patient, the difference in the mean shift between the two alignment methods along the left-right (X), anterior-posterior (Y), and inferior-posterior (Z) directions was less than 1 mm. The mean standard deviation of ten patient measurements for the direct image based and the contour based alignment methods were 0.6 mm vs. 0.7 mm, 1.2 mm vs. 1.2 mm, and 1.6 mm vs. 0.6 along the X, Y, and Z directions, respectively. Particularly, for four of ten patients, large deviations (> 2mm) occurred more frequently in the Z direction with the direct image alignment method, indicating larger measurement uncertainties when compared to the contour alignment method. To confirm this finding, we engaged additional four observers to perform the same analysis. Figure 2 shows the mean and standard deviation of translational shift along the X, Y, and Z directions for each alignment method.

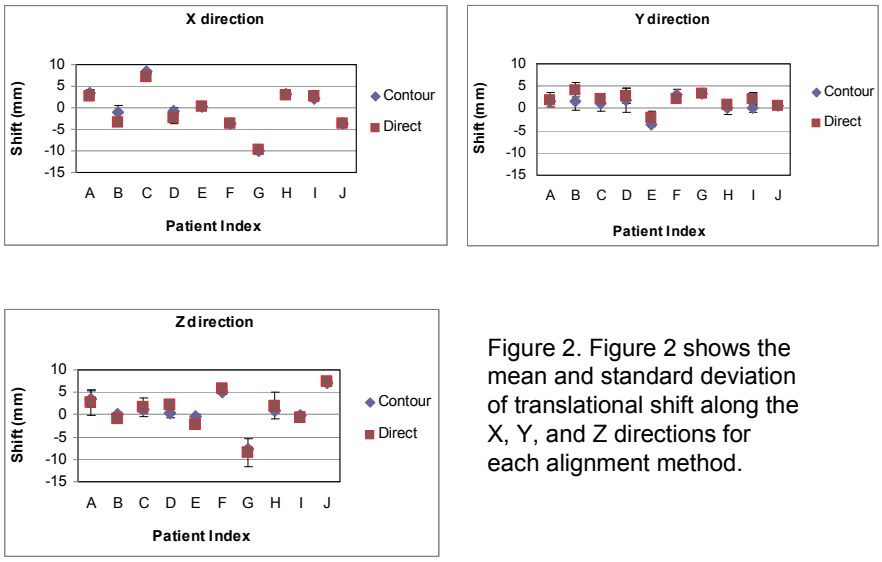

Figure 2. Figure 2 shows the mean and standard deviation of translational shift along the X, Y, and Z directions for each alignment method.

In conclusion, we found that the direct image based and contour based alignment methods are both reliable to detect translational setup errors for patients with prostate cancer. In the longitudinal direction, the measurement uncertainties are slightly increased with the direct image alignment method when compared to the contour alignment method. Since the manual adjustments are necessary for the both alignment methods, the results of this study may subject to inter-observer variations. Further study will investigate the effect of inter-observer variations between the two methods.

(c) A Proof of principle study

Because of the delay in obtaining approval of the IRB for this project, we conducted a proof of principle study for a patient, who received concurrent irradiation of the prostate and pelvic lymph nodes. In this study, we reported our initial findigs about using a novel adaptive strategy to address the challenge of independent movement of the two targeted volumes. For this particular patient, who has a horse-shoe abdominal kidney, a set of plans (referred to as multi-adaptive plans- MAP) was created with five presumed prostate positions. Under daily imaging guidance, a plan that was the closest to "the prostate position of the day" was chosen for treatment. Based on the seventeen available mega-voltage cone beam CTs, verification plans were retrospectively generated. For comparison, two additional sets of verification plans were also created using an MLC(mutli-leaf collimator)-tracking and the iso-tracking methods.

We found that for this patient, the prostate moved ≥ 0.5 cm superiorly in 11 of seventeen days. Of these days, 86% of the kidney volume would receive a daily dose < 0.8 Gy (20 Gy for the entire course treatment) on 6, 9, and 0 days for the MAP, MLC, and iso-tracking strategies, respectively. Accordingly, 95% of the prostate and pelvic lymph nodes would receive a daily dose $> 98\%$ of the prescribed dose on 10 , 17 , and 17 days, and on 14, 4, and 10 days for seventeen analyzed treatment days, respectively. With this proof of principle study, we concluded that the MAP approach is a clinically feasible. Verification plans calculated with daily

MV-CBCT provide patient specific dosimetric monitoring and dose guidance. The complete manuscript is in Appendix (b).

(d) Other software developments

According to the SOW task 2 item 1 and 2, we completed a computer program (with MATLAB) to transform the copied contours of the prostate into a series (eight of them) of presumed positions. Import these contours back to the treatment planning system (Pinnacle, Philips Medical solutions). We also completed another computer program that can efficiently extract defined dosimetric endpoints (such as doses to the 95% of the target volumes, doses to the 5%, 10% and 20% of the rectum, bladder, and small bowel, and the equivalent uniform doses to all structures) from numerous plans for the purpose of quantitative comparison. These two programs will facilitate our research project in the second year.

(e) Request of change of the research location

Since April 10, 2009, the PI has been transitioned to the Cleveland Clinic, as the head of medical physics in the Department of Radiation Oncology, Cleveland Clinic, Cleveland, Ohio. The department at the main campus (where the PI is located) is equipped with six state-of-the-art linear accelerators including the newest linear accelerators ARTISTE from Siemens, and the high resolution and high precision linear accelerators (Synergy-S and Synergy-R) from Elekta. In particular for prostate patients, the department offers four different imaging guidance technologies, including a three dimensional ultrasound image guidance system (Resonant Medcial's RESTITU), Calypso 4D localization system, Kilo-voltage cone beam CT, and MV-voltage cone beam CT.

About 400 prostate patients have been treated annually at the main campus of Cleveland Clinics of Radiation Oncology Department. For inter-median to high risk prostate cancer patients, concurrent treatments of the pelvic lymph nodes and prostate gland are delivered with either a large field size Elekta liner accelerator, or the newest Siemens linear accelerator. The large field size Elekta machine is equipped with KV-CBCT and a conventional MLC with a leaf width of 1 cm. The Siemens Artise machine is a newly developed linear accelerator by Siemens, equipped with MV-CBCT and a finer leaf width (0.5 cm) for the central field and a conventional leaf width (1 cm) for the outer field. The PI will continue her collaborations with co-investigators (Dr. Jean Pouliot and Dr. Mack Roach) at UCSF and establish a new collaboration at the Cleveland Clinic with Dr. Rahul Tendulkar, who is specialized in prostate cancer.

The scope of this research project and the statement of work will remain the same. In order to accomplish the research goal and tasks stated in the statement work, the PI requests the change of research location from UCSF to the Cleveland Clinic. In order to firm our collaboration and keep the continuity of the research project, the PI plans to sub-contract part of research components back to her previous institution (UCSF). We believe that the change of the research location of the PI will not negatively impact the research goals, instead will increase the impact of research in the clinical implementation since patients form both institutions will directly benefit from the success of this research project.

Key Research Accomplishments:

(a) We obtained IRB approval for conducting the proposed research and we also obtained sixteen patients' consents for the use of their treatment data in this research.
(b) An abstract related to task 1 (item 2 and 3) in SOW is accepted by the annual meeting of American Association of Physicists in Medicine (AAPM).
(c) Completed task 2 (item 1 and 2) in SOW.

Reportable Outcomes

(a) An abstract entitled as : "Study of Image Registration Methods Based on the Pelvic Bone and its Contour for Prostate Cancer Patient", Accepted by 2009 AAPM annual meeting. (Appendix a)
(b) An manuscript entitled as: " Management of Independent Movement of the Prostate and Pelvic Lymph Nodes: A Proof of Principle Study", to be submitted to International Journal of Radiation Oncology, Biology, and Physics (Appendix b)

Conclusion

In summary, in this initial period of research, we successfully obtained the IRB approval for the study and obtained consents from sixteen patients, who agreed to let us use their treatment data for the study. in order to determine detection accuracy of the patient setup error (and later to determine the magnitude of prostate movement), we analyzed accuracy of two image registration methods, referred to as direct image registration and contour based image registration. We found that the direct image based and contour based alignment methods are both reliable to detect translational setup errors for patients with prostate cancer. In the longitudinal direction, the measurement uncertainties are slightly increased with the direct image alignment method when compared to the contour based alignment method. Since the manual adjustments are necessary with the both alignment methods, the results of this study may subject to inter-observer variations. Further study will investigate the effect of inter-observer variations between the two methods.

We also conducted a proof of principle study and reported our initial data about the use of three adaptive strategies. We found that the proposed multiple adaptive plan (MAP) approach is a clinically feasible. Verification plans calculated with daily MV-CBCT can further provide patient specific dose guidance.

Despite the change of the PI's physical location and the delay in obtaining IRB approval, we accomplished task 1 (item 1, 2, and 3) and task 2 (item 1 and 2) form the statement of work. Our research timeline is on target. In order to accomplish all tasks and the research goal, we request a transfer of this research project from PI's previous institution (The university of California, San Francisco) to her current institution (Cleveland Clinic). We believe that this change will not negatively impact the research goals, instead will increase the impact of research in the clinical implementation since patients form both institutions will directly benefit from the success of this research project.

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(1) Ludlum E, Mu G, Weinberg V, Roach III M, Verhey L, and Xia P: "*An Algorithm for Shifting MLC Shapes to Adjust for Daily Prostate Movement during Concurrent Treatment with Pelvic Lymph Nodes*", **Med. Phys**. 34(12):4750-6 (2007).

Appendices

Appendix A

Abstract:

Study of Image Registration Methods Based on the Pelvic Bone and its Contour for Prostate Cancer Treatment

Peng Qi, Andrew Hwang, and Ping Xia

Purpose: Because of different imaging contrasts in the MVCBCT and the planning CT, image registration between the two modalities may introduce additional uncertainties in image guided radiotherapy (IGRT). For a group of ten prostate patients concurrently treated with the pelvic lymph nodes, we compared two alignment methods: one directly aligns the pelvic bone from the MVCBCT to that of the planning CT; the other aligns the pelvic bone from the MVCBCT to the contour of the pelvic bone from the planning CT.

Method and Materials: On the first day of treatment, the treatment positions for all patients were verified with an extended field of view (FOV) MVCBCT to include the entire pelvic bone. Subsequently, the reduced FOV-MVCBCT was used daily to localize the prostate with implanted markers. Only the FOV-MVCBCT was used to identify uncertainties in patient positioning. For each patient, the MVCBCT was manually registered with the two alignment methods. Each alignment method was repeated three times by a single observer in three separate times.

Results: For each patient, the difference of mean shift along the left-right (X), anterior-posterior (Y), and inferior-posterior (Z) directions was small between two alignment methods. The mean standard deviation of 10 patient measurements for the contour based and bone based registration were 0.6 mm vs. 0.7 mm, 1.2 mm vs. 1.2 mm, and 0.6 mm vs. 1.6 mm along the X, Y, and Z directions, respectively. Particularly, more large deviations (> 2mm), 4 out of 10 patients, were observed in the Z direction with the bone based registration method.

Conclusion: The contour based image registration method achieved more consistent measurement than the bone based registration in verification of the treatment position for prostate patients concurrently treated with pelvic lymph nodes.

Appendix B

Management of Independent Movement of the Prostate and Pelvic Lymph Nodes: A Proof of Principle Study

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Conflict of interest: None

ABSTRACT

Purposes: Concurrent irradiation of the prostate and pelvic lymph nodes poses a technical challenge due to the independent movement of the two targeted volumes. In this paper, we reported our first clinical experience of using a novel adaptive strategy to address this issue.

Methods/Materials: For a patient with a horse-shoe abdominal kidney, a set of plans was created with five presumed prostate positions. Under daily imaging guidance, a plan that was closest to "the prostate position of the day" was chosen for treatment. Based on the seventeen available mega-voltage cone beam CTs, verification plans were retrospectively calculated. For comparison, two additional sets of verification plans were also created for an MLC-tracking and the iso-tracking methods.

Results: For this patient, the prostate moved ≥ 0.5 cm superiorly in 11 of seventeen days. Of these days, 86% of the kidney volume would receive a daily dose < 0.8 Gy (20 Gy for the entire course treatment) on 6, 9, and 0 days for the MAP, MLC, and ISO-tracking strategies, respectively. Accordingly, 95% of the prostate and pelvic lymph nodes would receive a daily dose > 98% of the prescribed dose on 10 , 17 , and 17 days, and on 14, 4, and 10 days for seventeen analyzed treatment days, respectively.

Conclusions: The MAP approach is a clinically feasible strategy. Verification plans calculated with daily MV-CBCT provide patient specific dosimetric monitoring and dose guidance.

Keywords: Adaptive radiotherapy, Prostate cancer, Intensity-modulated radiotherapy, and Image-guided radiotherapy.

INTRODUCTION

Although the prophylactic irradiation of lymph nodes is routine practice for many cancer sites, the role of pelvic lymph node irradiation is controversial in the treatment of men with localized prostate cancer. Since the initial reports in the 1980s [1, 2], the typical four-field treatment technique for pelvic irradiation has largely remained unchanged. With this conventional technique, the benefit and risk of pelvic irradiation has been debated for more than two decades [1, 3-5]. Using a novel magnetic resonance lymphangiographic technique, Shih et. al.[6] showed that the conventional field borders defined according to the bony anatomy inadequately include the pelvic lymph nodal regions, resulting in a poor radiation dose coverage [7]. Despite this inadequate dose coverage, investigators from the Radiation Therapy Oncology Group (RTOG) have still demonstrated advantage of progression free survival with prophylactic pelvic nodal lymph irradiation[8].

Intensity Modulated Radiotherapy (IMRT) has been shown significant clinical advantages over conventional and three-dimensional conformal radiotherapy (3DCRT) when treatment is limited to the prostate [9, 10]. There is also a growing body of data [7, 11] suggesting that IMRT provides even greater advantages when pelvic nodes are being irradiated. For the concurrent treatment of the prostate and pelvic lymph nodes, one [7] of our previous studies reported that IMRT plans not only significantly improved the dose coverage to the pelvic lymph nodes, but also greatly reduced the doses to the rectum, bladder, and the small bowels. However, this concurrent treatment of the prostate and the

pelvic lymph nodes poses a new technical challenge due to the independent movement of the prostate and the pelvic lymph nodes,

Movement of the prostate has been well documented[12]. It varies from a few millimeters up to 1.5 cm in relative to the pelvic bones [13, 14]. The pelvic lymph nodes, on the contrary, are relatively fixed in close proximity to vascular structures[6], which are presumably fixed with respect to bony anatomy[15]. This independent movement of two targeted volumes renders the conventional isocenter shifting method inadequate. Addressing this problem by simply adding a large planning margin to ensure adequate coverage of the target volumes unavoidably results in the inclusion of normal structures in the high dose area of the radiation fields, potentially increasing the risk of normal tissue complications.

The ideal approach to resolve this challenge is on-line re-planning on a daily basis, but because of extended planning time, on-line re-planning is not practical with current technology. Without requirement of on-line dose re-calculation, we proposed a MLC leaf-shifting algorithm to provide an alternative solution [16]. The clinical implementation of this MLC-shifting approach requires a new feature in the Record & Verify System, which will allow users to adjust the MLC leaf positions efficiently at the treatment console. To circumvent this obstacle, we propose a novel and practical strategy by creating a pool of IMRT plans to accommodate multiple presumed prostate positions. This strategy is referred to as the multiple adaptive plan (MAP) IMRT. In this paper, we report our initial experience of applying the MAP-IMRT approach to a special patient, and compared this strategy to the MLC-tracking and the conventional iso-tracking methods by applying the delivered beams to the daily mega-voltage cone beam CT.

MATERIALS AND METHODS

a. *Multiple Adaptive plan strategy*

The multiple adaptive plan IMRT (MAP-IMRT) strategy creates a pool of IMRT plans, each individually optimized to accommodate a presumed prostate position. Based on the established prostate motion pattern [12-14], we created a pool of plans to compensate for prostate movements of 0.5 cm and 1.0 cm in the posterior and superior directions. The shifted prostate contours were created using an in-house program that read in the coordinates of the original prostate contours and shifted the coordinates of the contour to the presumed positions. These shifted prostate contours were input back to the treatment planning system (Pinnacle, version 7.6, Philips Medical Systems, Milpitas, CA) and appended in the set of planning contours for the patient. The initial IMRT plan for the patient was created based on our established planning protocol. Since the rectum and bladder were not shifted with the prostate, the anatomic relationship of these two organs with the shifted prostate was invalidated, rendering the initial planning dose constraints to the rectum and bladder irrelevant. To address this problem, we constructed an artificial rind structure [17] around the shifted prostate to guide the planning system to produce highly conformal plans, thus effectively protecting the rectum and bladder.

b. MLC-tracking strategy

The MLC-tracking strategy is based on our previously proposed leaf-shifting algorithm [16], which can track the movement of the prostate while not significantly affecting dose distributions to the pelvic lymph nodes. Briefly, based on the magnitude

and direction of the daily prostate movement, the algorithm was designed to adjust the positions of selected MLC leaf pairs to track the translational motion of the prostate for each beam. The algorithm assumes the prostate is a rigid body and the rotational motion is negligible, therefore, the online dose calculation is not required by simply keeping the distance between each leaf pair unchanged. Clinical implementation of this strategy is not ready yet as it requires a new feature in the Record & Verify System to allow efficient adjustment of MLC leaf positions at the treatment console.

c. Clinical Implementation

A 70 year old patient with high risk prostate cancer known to have nodal metastasis adjacent to a "horse-shoe" abdominal kidney was treated with the MAP-IMRT strategy. Prior to radiotherapy, three markers were implanted in the base, middle, and apex of the prostate. The patient was simulated in a supine position with an empty rectum and full bladder. The treatment planning CTs was acquired with 3 mm slice thickness. Pelvic lymph node volumes were delineated to include obtrurator, external/internal iliac, common iliac, and presacral lymph nodes with 1.0-2.0 cm expansion, up to the vertebral level of L5-S1. Rectal volumes were contoured from the anus at the level of the ischial tuberosities to the sigmoid flexure. The bowel volumes (including the colon, large and small bowels) were contoured to include abdominal space.

The patient was treated with two phase IMRT planning. Phase I involved concurrently treating the prostate to 50 Gy and pelvic nodes to 45 Gy in 25 fractions, followed by a boost dose to the prostate in Phase II. A major dosimetric consideration for this particular patient was to minimize the dose to the kidney during Phase I treatment.

Although the concept of MAP-IMRT can accommodate the prostate movement in any or multiple directions, we decided to use only five MAP-IMRT plans for this early clinical implementation for practicality. These MAP-IMRT plans accommodated the prostate movement in the posterior and superior directions with a planning margin of 0.2 cm. The planning margin in the anterior and inferior directions was enlarged from 0.2 cm to 0.5 cm and the panning margin in the lateral direction was 0.2 cm. The planning margin for the pelvic lymph nodes was 0.5 cm.

d. Image Guidance and Treatment Delivery

Prior to each treatment, a mega-voltage cone beam CT (MV-CBCT) was acquired, using a commercial system (MVision^{TM} , Siemens Medical Solutions, Concord, CA). The MV-CBCT was reconstructed from 200 projection images acquired with a total of 2 MU. The program automatically registers the planning CT and the MV-CBCT according to the image intensity and calculates the required couch shifts to align the two image sets. In order to implement MAP-IMRT, the prostate displacement related to the pelvic bones was determined by two successive alignments, one aligned to the pelvic bones and the other aligned to the implanted markers. The couch shifts obtained from the bony alignment were the setup error and were corrected subsequently by shifting the treatment couch. The prostate displacement of the day, relative to the pelvic bony, was determined by the difference between the shifts given by the two alignments. Based on the prostate position of the day, the IMRT plan in which the planned prostate position was best matched with the actual prostate position, was chosen by the therapist according to a plan selection instruction.

e. Relative Treatment Dose Comparison and Analysis

With acquired daily MV-CBCT, we calculated the delivered dose to the patient anatomy of the day. Because of limited soft tissue contrast of low dose (2MU/scan) MV-CBCT, we transferred contours from the planning CT to assess daily dose to organs of interest. While we are under development to calibrate the CT density and to correct for the cupping effect of the MV-CBCT, we assigned a CT density of 1 g/cm^3 to all tissue and used the external contour of the planning CT to supplement the missing tissue (also assigned to a CT density of 1 g/cm^3) due to the limited field of view with the current MV-CBCT acquisition system. With these approximations, the dose distributions calculated on MV-CBCTs were used for relative dose comparison with intended plans for this proof of principle study.

i. Contour transfer

Each MV-CBCT was input into the Pinnacle planning system for the relative treatment dose comparison. Each MV-CBCT was set as the primary images, and fused with the planning CT. An in-house program was written to allow the contoured planning structures to be input with the planning CT into the Pinnacle system. Assuming a stationary relationship between the pelvic lymph nodes and pelvic bones, the pelvic lymph nodal volume was transferred from the planning CT to the MV-CBCT after a rigid body image fusion by aligning the pelvic bony structures. During the treatment, the prostate position in relative to the pelvic bones was determined by a dual alignment procedure (as described above) and only translational shifts were recorded. The image

registration tool provided by the Pinnacle system automatically utilized translation and rotation transformation. To evaluate the dose delivered to the patient, we used our in-house program to make translational shifts of the prostate according to the detected position and input this shifted contour as the prostate of the day into the corresponding MV-CBCT.

ii. Verification Plans

Three sets of verification plans were generated and compared. The first set of verification plans was created according to the MAP-IMRT strategy; the second set was based on the MLC-tracking strategy; and the third set utilized the conventional iso-tracking method by simply shifted the iso-center to follow the prostate movement. For each MAP verification plan, the delivered plan of the day was directly applied to the corresponding MV-CBCT of the day.

In each MLC-tracking plan, the affected MLC positions in all segments from the original IMRT plan (the plan for un-shifted prostate position) were moved to track the prostate position of the day. The resultant dose distribution of each MLC-tracking plan was calculated on the corresponding MV-CBCT of the day. For each iso-track plan, the treatment iso-center was shifted according to the detected prostate displacement of the day and the MLC segments from the original plan were again applied to the MV-CBCT of the day with the shifted iso-center.

RESULTS

a. MAP-IMRT plans

A set of five individually optimized IMRT plans, referred to as MAP-IMRT plans, was prepared and approved for the treatment of this patient. Fig. 1 shows the five different prostate positions, displayed in the posterior and superior directions in 0. 5 cm increments. Table I lists association of the directions and magnitudes of prostate movement with the five MAP-IMRT plans and the clinical usage of each plan for 17 treatment days. A typical iso-dose distribution of each plan was depicted in Fig. 2a in an axial image, demonstrating excellent dose conformity for each scenario. The corresponding dose volume histograms (DVHs) were displayed in Figs. 2b-c for the PTV, pelvic lymph nodes, small bowel, and kidney. The DVHs of the MAP-IMRT plans were slightly different from each other because the optimal solution found by the computer was slightly different for each scenario. According to the usage of the each plan during delivery, the weighted average DVHs for the PTV, pelvic lymph nodes, small bowel, and kidney were compared to the original plan with unshifted prostate (Fig. 2d). The weighted averaged DVHs were obtained by first binning all DVHs in the same bin size, then averaging them with a relative weighting factor according to the usage of each plan recorded during delivery. As shown in Fig. 2d, the weighted average DVHs were similar to the original plan, indicating the utility of MAP plans.

b. Image guidance

Fig. 3 shows a typical alignment of the MV-CBCT using the pelvic bony anatomy and a typical alignment of the MV-VBCT using the implanted markers. For this treatment day, the setup error determined by aligning to the pelvic bones was 0.3 cm, 0.3 cm and 0.5 cm along the lateral, vertical and longitudinal directions, respectively. After subtraction of the two alignments, the prostate motion was 0.5 cm posterior relative to the

pelvic bony anatomy. Based on the seventeen MV-CBCT acquired for this patient, the prostate moved 0.4-0.7 cm superior in 38% of treatment days, > 0.8 cm superior in 19%, 0.4-0.7 cm posterior in 12%, and less than 0.3 cm in all directions in 31%. Seven of 17 days had a setup error greater than 0.5 cm in any direction while the remaining days had a setup error less than 0.5 cm in any direction. Setup error in any direction > 0.1 cm was corrected. Fig. 4 shows the detected daily setup errors and the prostate movements along the three major axes. For this specific patient, the prostate movement was not random, shifted in the superior direction in the more than 50% of the treatment days.

c. Dose verification with MV-CBCT

Figs. 5a-b depict the prostate contour of the day transferred from the planning CT to the MV-CBCT by rigidly registering implanted markers. Similarly, the pelvic lymph node contours were transferred by rigidly registering the pelvic bones. Because of the limited field of view of our MV-CBCT, the outline of external tissue was also transferred by rigidly registering of the pelvic bones to compensate for the missing tissue in the MV-CBCT. On that selected treatment day, the prostate moved 0.5 cm superior. In addition, Fig. 5a shows the dose distribution calculated by applying the chosen treatment plan of the day to the MV-CBCT. For comparison, Fig. 5b shows the dose distribution calculated using the MLC-tracking strategy. Compared to the MAP-tracking method, MLC-tracking overly compensated the superior movement of 0.5 cm because of the limitation of MLC leaf width. Fig. 6 shows the details of the dose to 95% of the prostate (D95) calculated based on daily MV-CBCT. The D95s of the MAP-tracking were the delivered daily dose calculated based on the chosen plan of the day, compared to the D95 of the MLC-tracking and ISO-tracking methods. As expected, the iso-tracking method followed the

prostate movement and achieved an excellent dose coverage to the prostate for these 17 treatment day. Because of limited number of MAP-IMRT plans available, only one prostate movement direction could be compensated when the prostate moved in both superior and posterior directions. On the fifteenth treatment day, the detected prostate movements were 1.2 cm superiorly and 1.2 cm anteriorly and the large superior shifted MAP-IMRT plan was chosen for the treatment. A similar situation occurred on the fifth treatment day.

Based on the dose calculated on the daily MV-CBCT, Fig. 5 shows the dose to 95% of the pelvic lymph nodes (D95). The MAP-tracking achieved adequate dose coverage to the pelvic lymph nodes while the iso-tracking method resulted in under-dosing the pelvic lymph nodes on 4 out of 17 treatment days analyzed. The MLC-tracking method also resulted in slight under dosing of the pelvic lymph nodes due to the finite MLC leaf width, which is unable to compensate for superior-inferior prostate movements less than the leaf width.

For the kidney, we used the endpoint of V20, percentage volume received more than 20 Gy, to evaluate the three different strategies. As shown in Fig. 6, the ISO-tracking method increased the V20 >15% for most of treatment days, while both MLC-tracking and MAP-tracking methods kept the V20 <15% for most of treatment days.

DISCUSSION

Under daily image guidance, the current study reported our first clinical experience of applying a novel concept of multiple IMRT plans to accommodate independent movement of the prostate and pelvic lymph nodes. To our knowledge, this

study is the first to report on the clinical implementation of an adaptive strategy to account for the varied anatomic relationship between the prostate and pelvic lymph nodes. Although clinical implementation of this adaptive strategy at the current stage is still rather laborious, this study provided a "proof of principle". Despite the laborious effort, it is clinically justified for this very special case, in a patient with high risk prostate cancer with evidence of pelvic lymph nodal involvement, who also required special attention to protect his only abdomen kidney This approach can potentially extend to other thoracic and abdominal malignancies.

A recent simulation study [15] indicated that one can simply ignore the problem of independent movement of the prostate and pelvic lymph nodes, based on an assumption of a random movement of the prostate. Other studies [18-20] including the current study, however, demonstrated that prostate movement may not necessarily be random but depends on the shapes of the rectum and bladder during acquisition of the planning CT [18-20]. Adding a large planning margin around the pelvic lymph nodes is another solution. For most patients, this enlarged planning margin could result in increased bowel toxicities, including sever diarrhea. For the special patient reported in this study, this enlarged planning margin could result in detrimental renal toxicity since the kidneys are near the involved lymph nodes.

With advancement of imaging technology and computer optimized treatment planning, we anticipated that it is possible to acquire daily CT image sets and to develop the ideal strategy of on-line re-planning on a daily basis. Some researchers have worked

to develop deformable image registration to improve efficiency of structure delineation [21-23] while others have sought to develop fast dose calculation engines and fast computer optimization algorithms [24-26]. For prostate only treatment, our clinical experience and other published studies [27, 28] support that the iso-center tracking strategy is practical and effective. However, as indicated in the current study, this strategy fails to compensate for the pelvic lymph nodes because of the independent movement of the two volumes. The other two strategies investigated in this study were not ideal. The multiple IMRT plans approach can only prepare for a few presumed prostate positions. The MLC shifting method has limited resolution in the longitudinal direction.

Future study is needed to streamline the process of creating multiple plans, including the ability to create multiple prostate positions within the treatment planning CT. Until the development of the capability of on-line MLC shifting, one can apply the MLC-tracking algorithm to create MAP plans for prostate motions in non-longitudinal directions. Because of the limitation of the finite MLC width, the MAP plans to compensate for the longitudinal displacements will be created by individually optimization. With this streamlined planning, one may apply the MAP IMRT strategy to more patients.

CONCLUSIONS

Although online re-planning may be the ideal strategy to accommodate independent movement of the prostate and pelvic lymph nodes during concurrent treatment, re-optimizing a set of IMRT plans with multiple prostate positions is more

clinically feasible and practical. The conventional iso-center shifting method is inadequate for selected cases where the concurrent treatment of the prostate and pelvic lymph nodes is limited by normal tissue tolerance. With improved record and verification system, the MLC tracking approach can further improve accommodation of prostate motion in the multiple directions. Combination of the MLC-track and MAP-IMRT strategies can minimize the limitation of the finite MLC leaf width in the longitudinal direction. Verification plans were calculated with daily MV-CBCT as a dosimetric monitoring tool provide patient specific dose guidance, allowing us to adjust radiation dose in the boost phase of the treatment.

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Figure Captions

Fig. 1 Five presumed prostate positions, hypothetically moved in the posterior and superior directions with 0.5 cm increment.

Fig. 2. (a) A typical iso-dose distribution of each plan of MAP-IMRT plans displayed an axial image. (b) The corresponding dose volume histograms for the PTV and pelvic lymph nodes. (c)The corresponding dose volume histograms (DVHs) for the small bowel and kidney. (d) According to the usage of the each plan during delivery, the weighted DVHs for the PTV, pelvic lymph nodes, small bowel, and kidney were compared to the original plan with unshifted prostate.

Fig. 3. For a selected MV-CBCT, a typical alignment of MV-CBCT with the pelvic bones (on the top panel) and a typical alignment of MV-VBCT with the implanted markers (on the bottom panel).

Fig. 4. The detected daily setup errors and the prostate movements along the three major axes for the seventeen treatment days.

Fig. 5. (a) The dose distribution (in isodose lines of 58 Gy-orange, 50 Gy-red, and 45 Gy -blue) calculated by applying the chosen treatment plan of the day to the corresponding MV-CBCT. (b) The dose distribution calculated by using the MLC-tracking strategy. The prostate contour (in solid blue) of the day was transferred from the planning CT to the MV-CBCT by rigidly registering implanted markers. The pelvic lymph node contours (in solid yellow) was transferred by rigidly registering of the pelvic bones. Because of limited field of view with our current MV-CBCT program, the outline of external tissue

(the outer line in light blue) was also transferred by rigidly registering of the pelvic bones to compensate for the missing tissue in the MV-CBCT.

Fig. 6. (a) The dose to 95% of the prostate (D95) calculated based on daily MV-CBCT for the iso-tracking, MAP-tracking, and MLC-tracking strategies; (b) The dose to 95% of the pelvic lymph nodes (D95) calculated based on daily MV-CBCT for the three strategies; (c) The percentage volume receiving more than 20 Gy for the corresponding strategies.

Table I: MAP-IMRT plans and its clinical usage for 17 treatment days

Plan type	Normal Plan	Small Posterior Shifts	Large Posterior Shifts	Small Superior Shifts	Large Superior Shifts
shifts	< 0.3 cm*	(0.4 – 0.7 cm)	(0.8-1.3 cm)	(0.4 – 0.7 cm)	(0.8 – 1.3 cm)
usage 6		1	0	7	3

* Shifts < 0.3 cm in all directions, or shifts dominantly in inferior or anterior directions

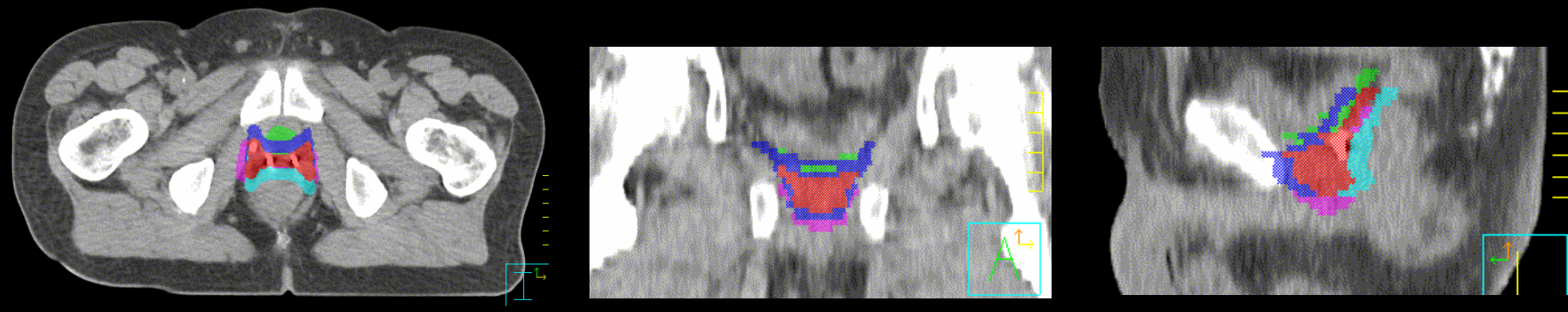
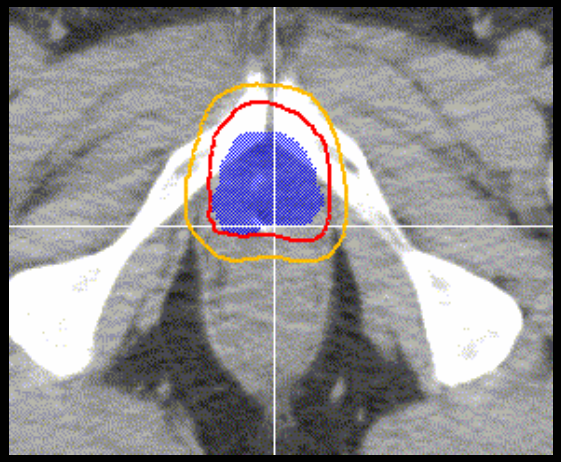
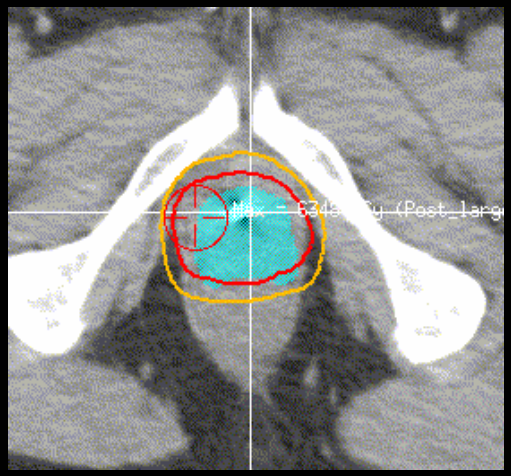


Fig. 1

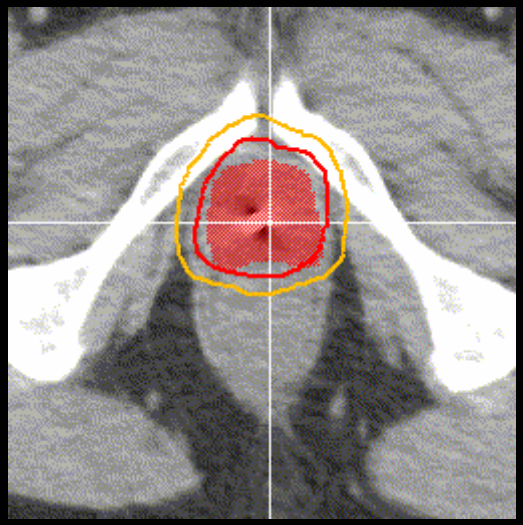
Move Anterior

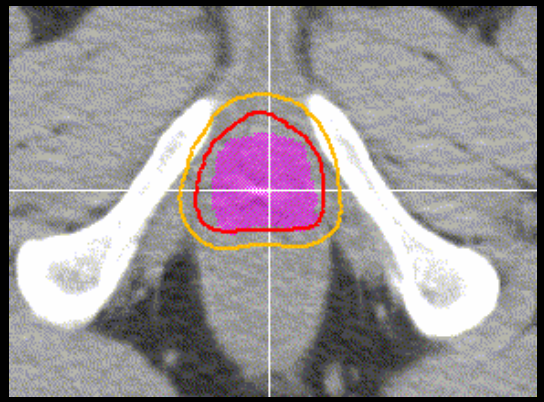


Move Posterior



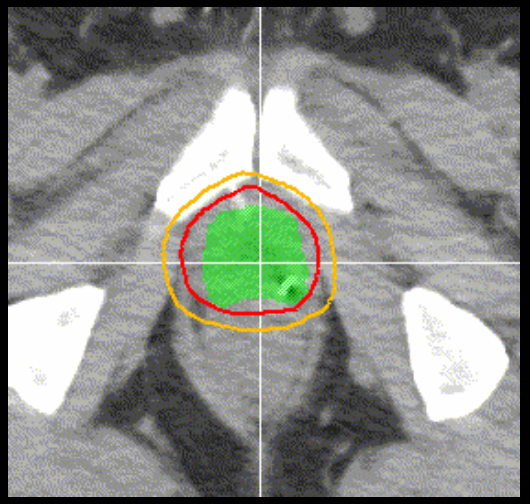
Un-shifted





Move Inferior

50 Gy, 45 Gy



Move Superior

Fig.2a

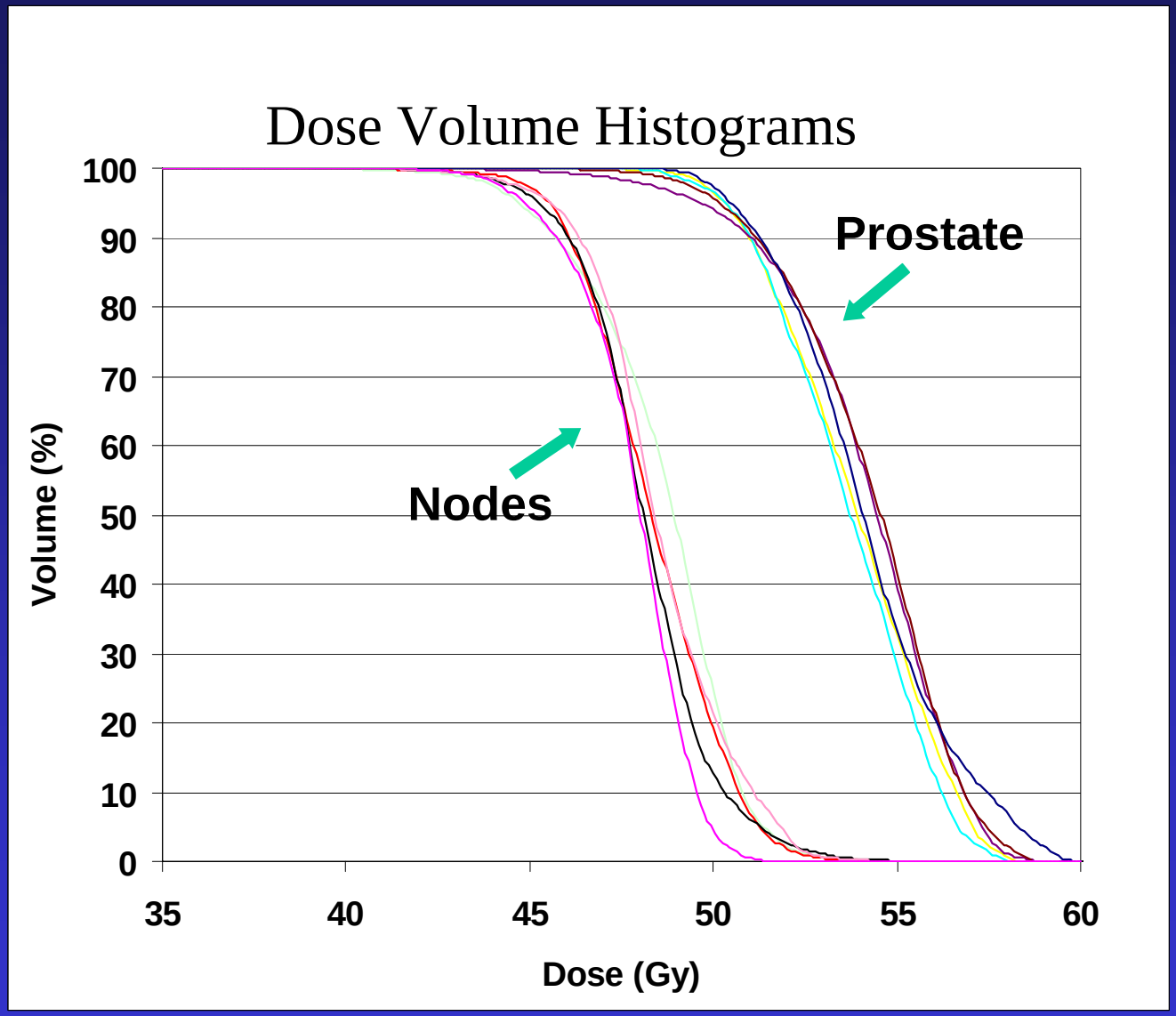

Dose Volume Histograms
Volume (%)
100
90
80
70
60
50
40
30
20
10
0
35
40
45
50
55
60
Dose (Gy)
Prostate
Nodes

Fig. 2b

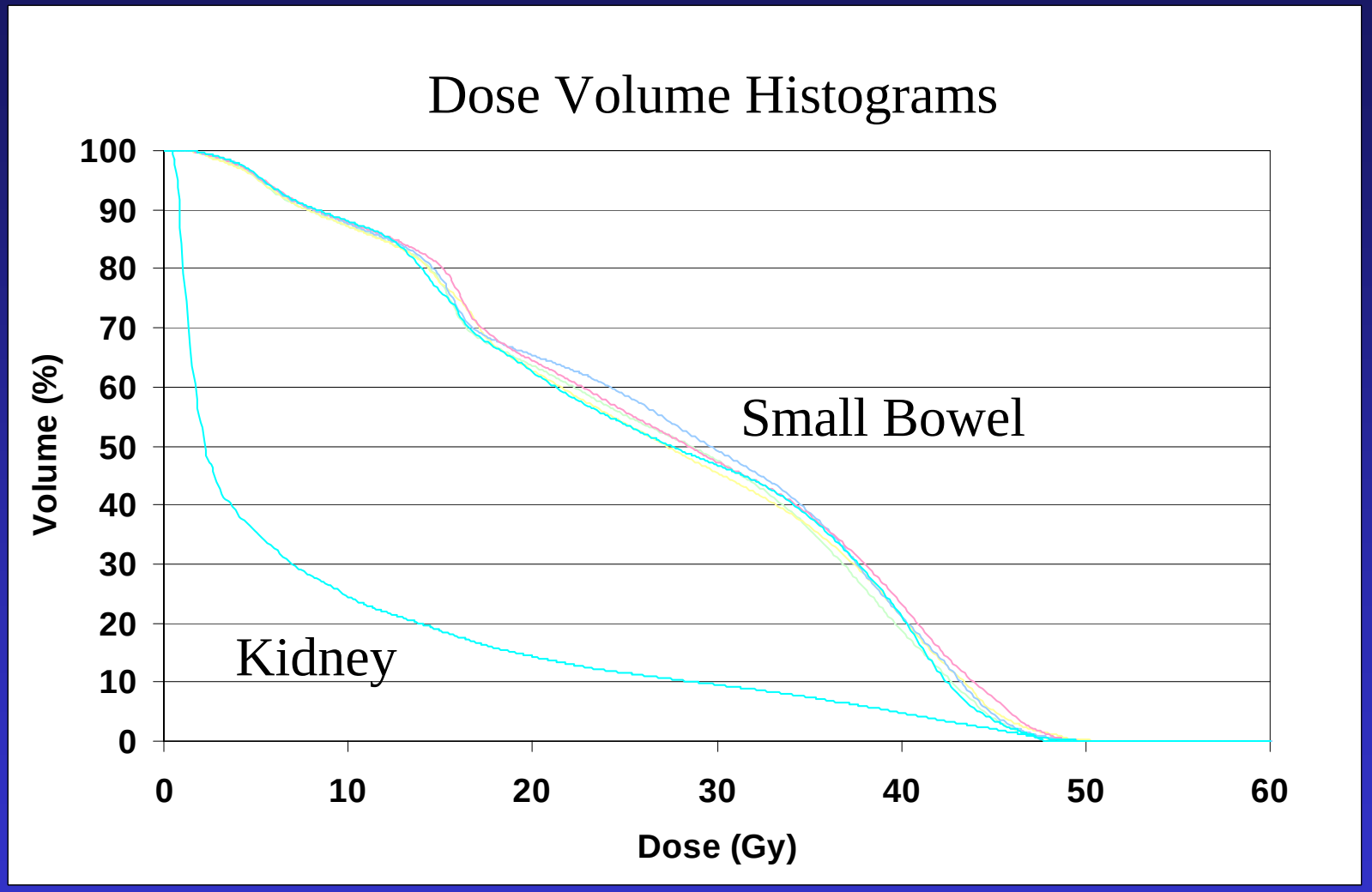

Dose Volume Histograms
Volume (%)
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
Dose (Gy)
Small Bowel
Kidney

Fig. 2c

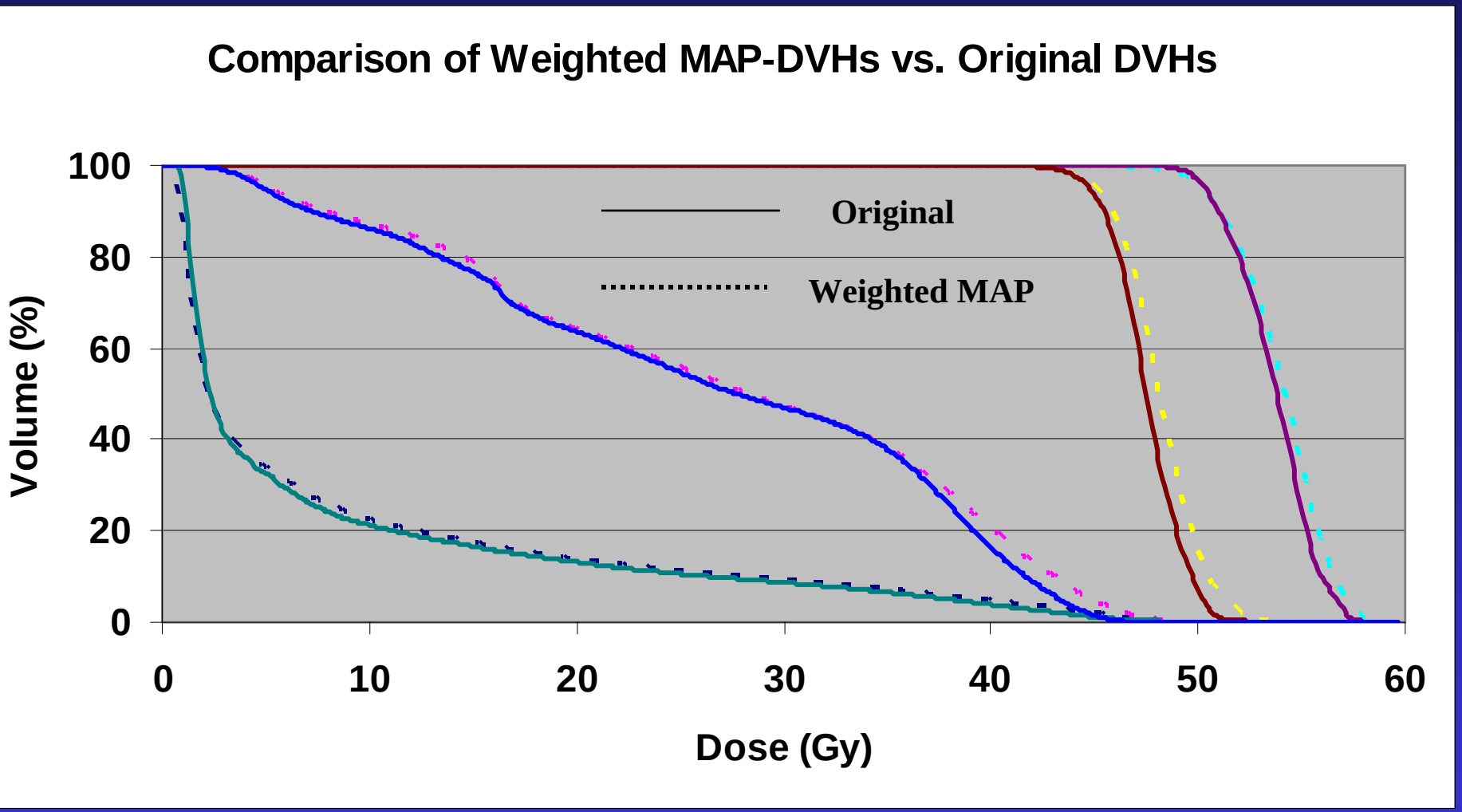
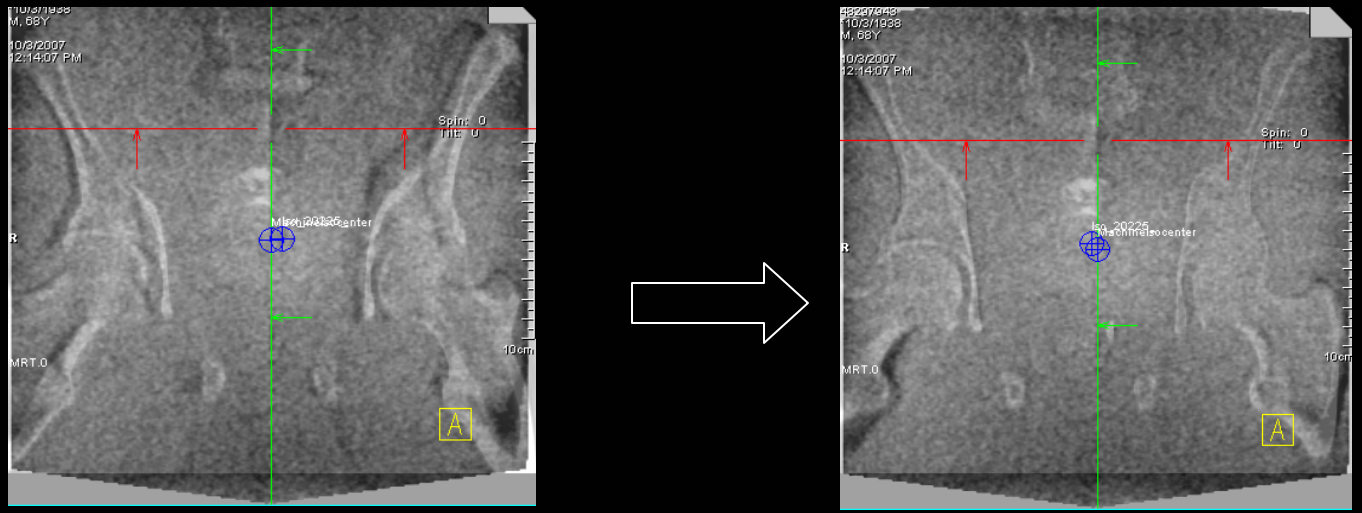
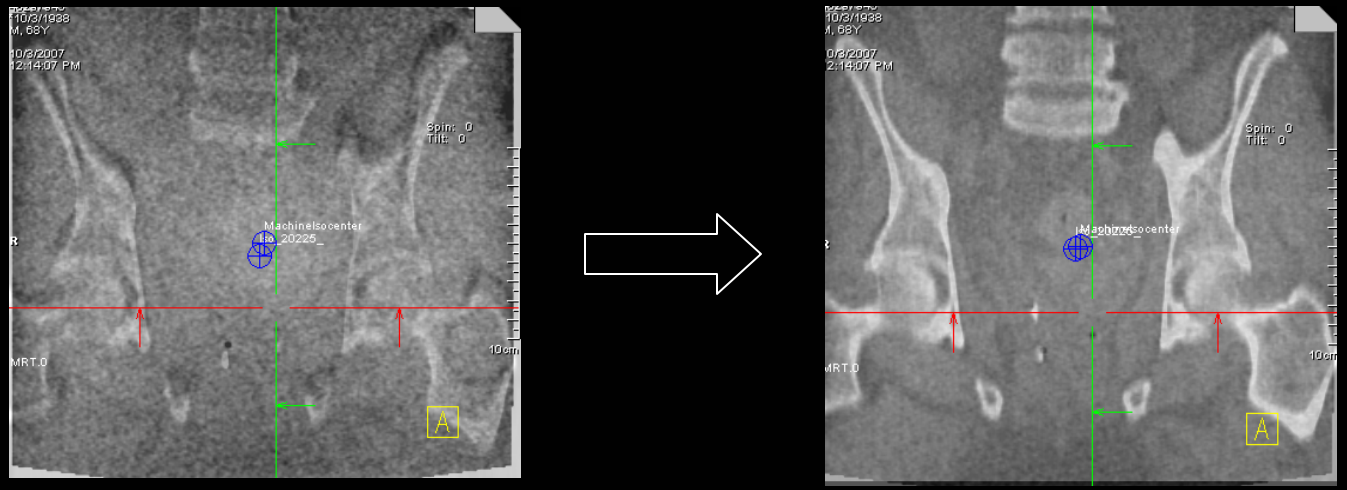

Comparison of Weighted MAP-DVHs vs. Original DVHs
Volume (%)
100
80
60
40
20
0
0
10
20
30
40
50
60
Dose (Gy)
Original
Weighted MAP

Fig. 2d



X_b=0.3cm
Y_b=0.3 cm
Z_b=0.5 cm

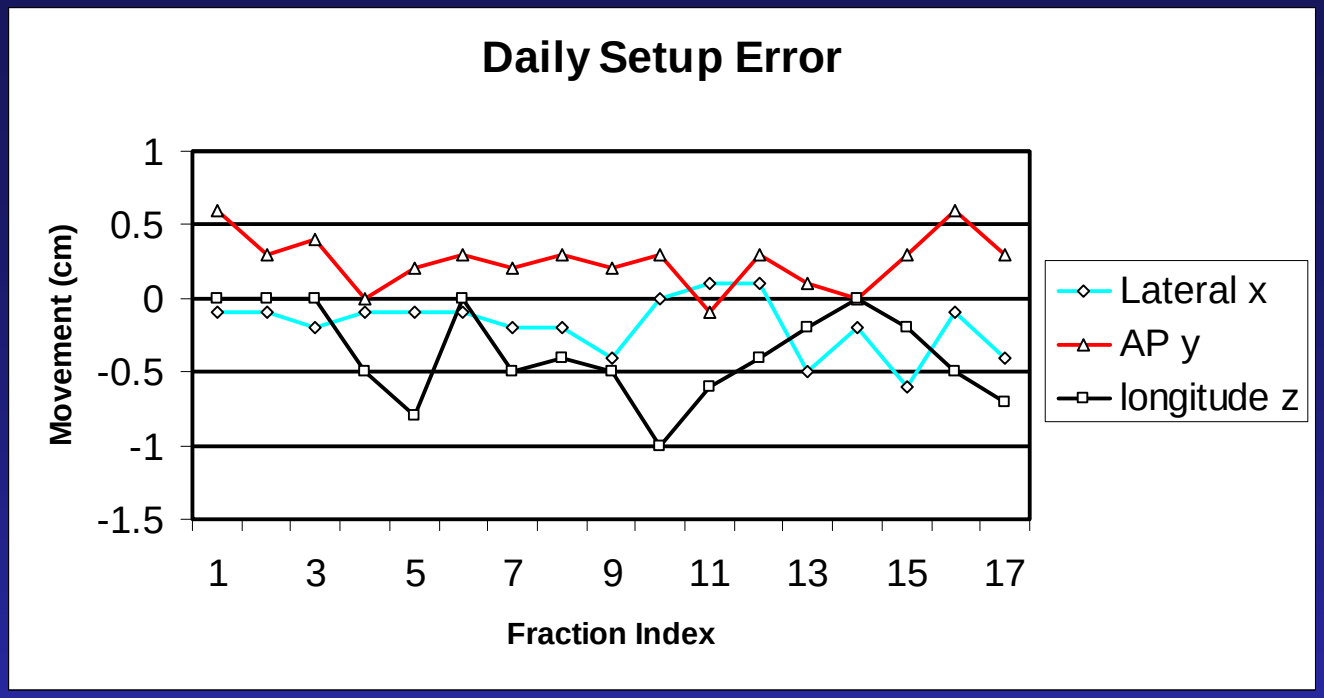
Bony Alignment



X_m=0.3cm
Y_m=0.5 cm
Z_m=0.5 cm

Marker Alignment

Fig. 3


Daily Setup Error
Movement (cm)
1
0.5
0
-0.5
-1
-1.5
1
3
5
7
9
11
13
15
17
Fraction Index
Lateral x
AP y
longitude z

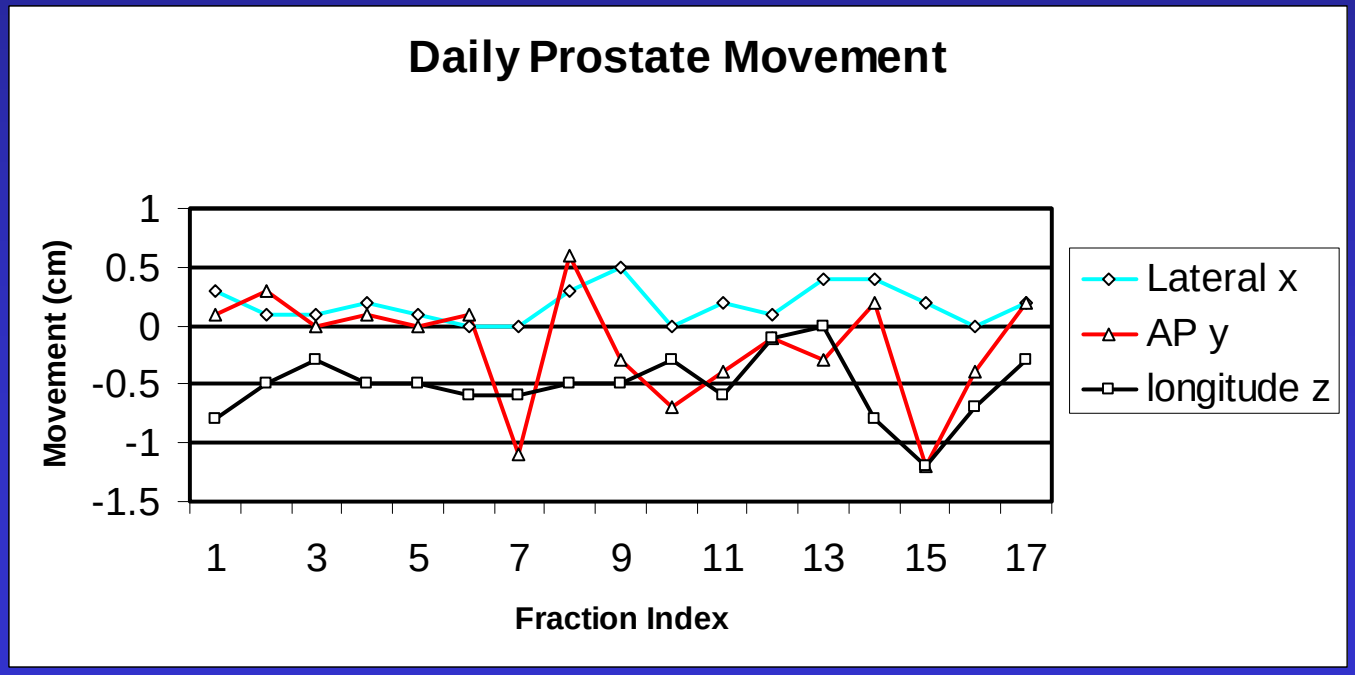
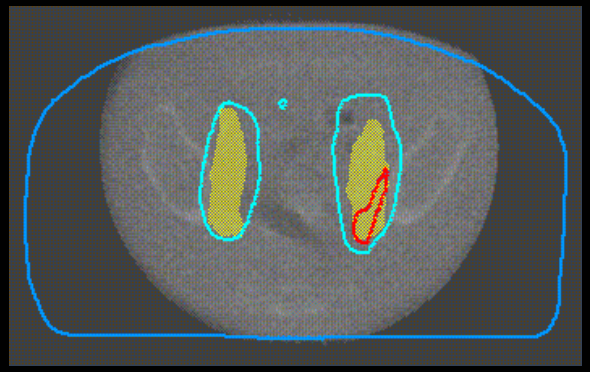
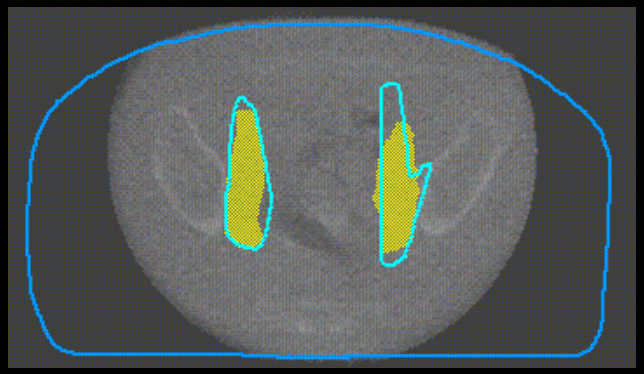
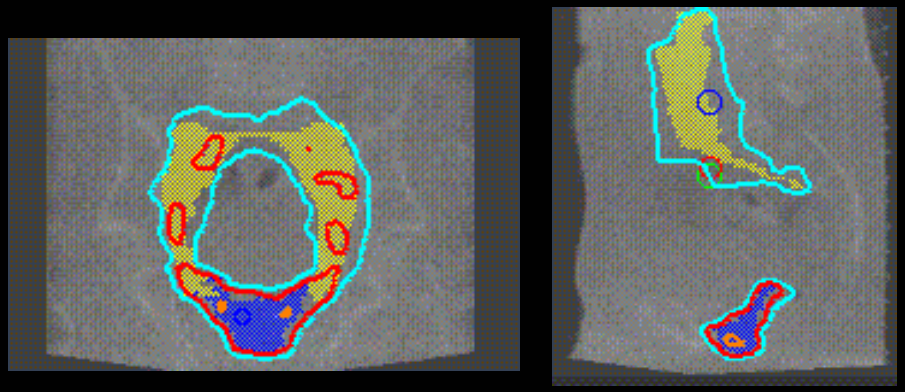

Daily Prostate Movement
Movement (cm)
1
0.5
0
-0.5
-1
-1.5
1
3
5
7
9
11
13
15
17
Fraction Index
Lateral x
AP y
longitude z

Fig. 4

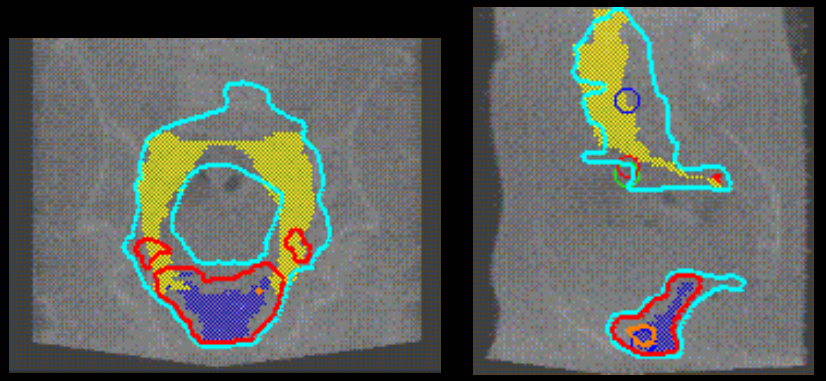


58 Gy
50 Gy
45 Gy





(a)



(b)

Fig. 5

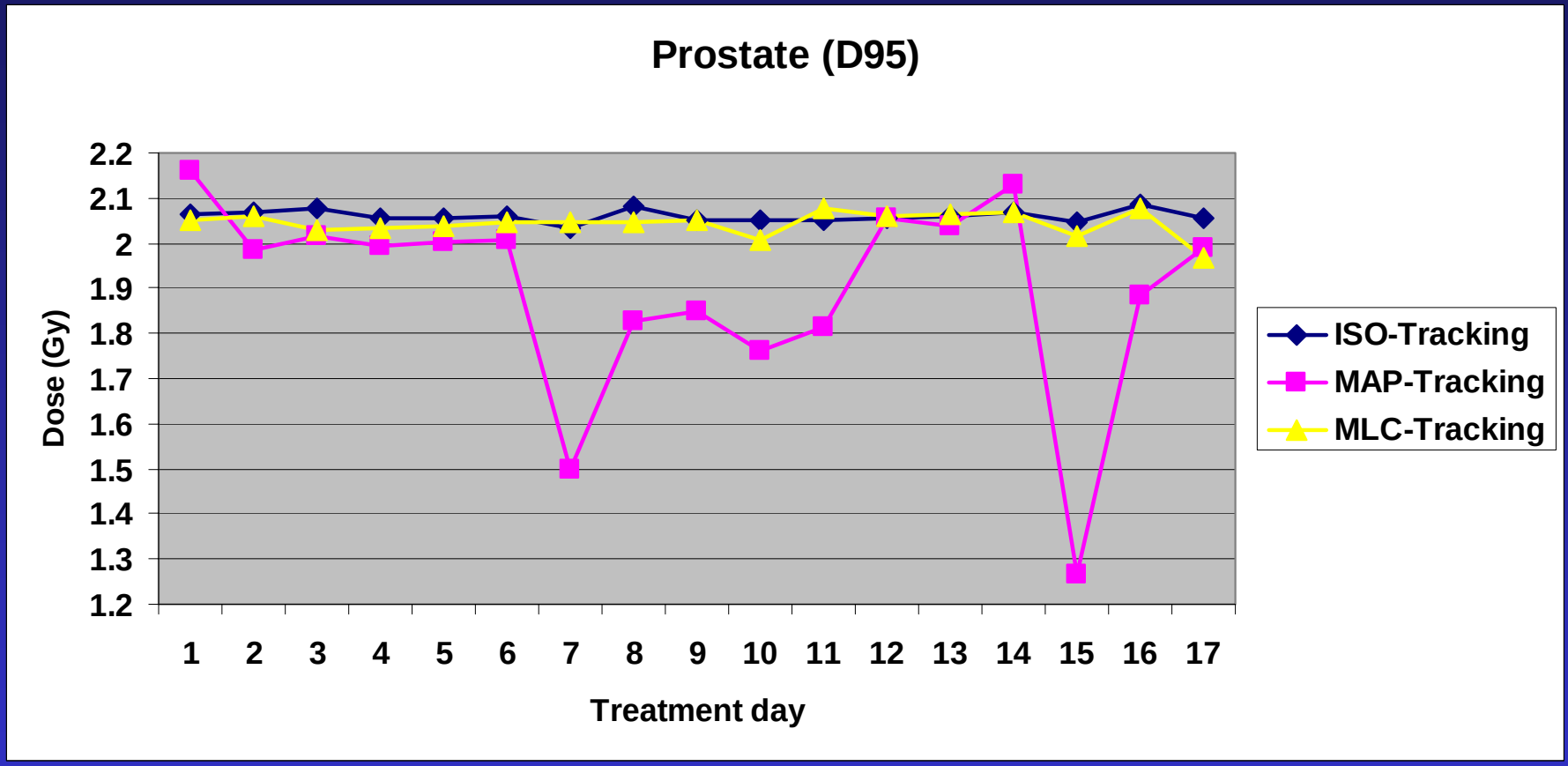

Prostate (D95)
Dose (Gy)
2.2
2.1
2
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
Treatment day
ISO-Tracking
MAP-Tracking
MLC-Tracking

Fig. 6a

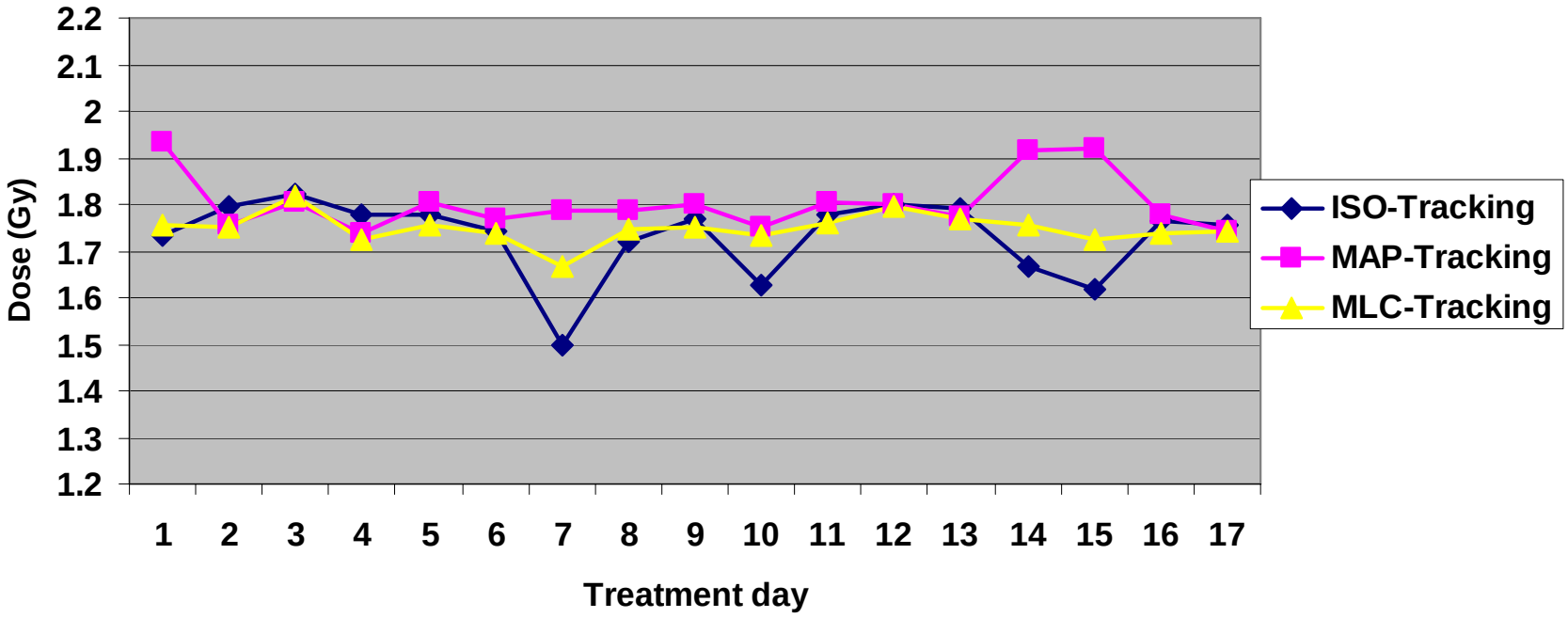

Pelvic Lymph Nodes (D95)
Dose (Gy)
2.2
2.1
2
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
Treatment day
ISO-Tracking
MAP-Tracking
MLC-Tracking

Fig. 6b

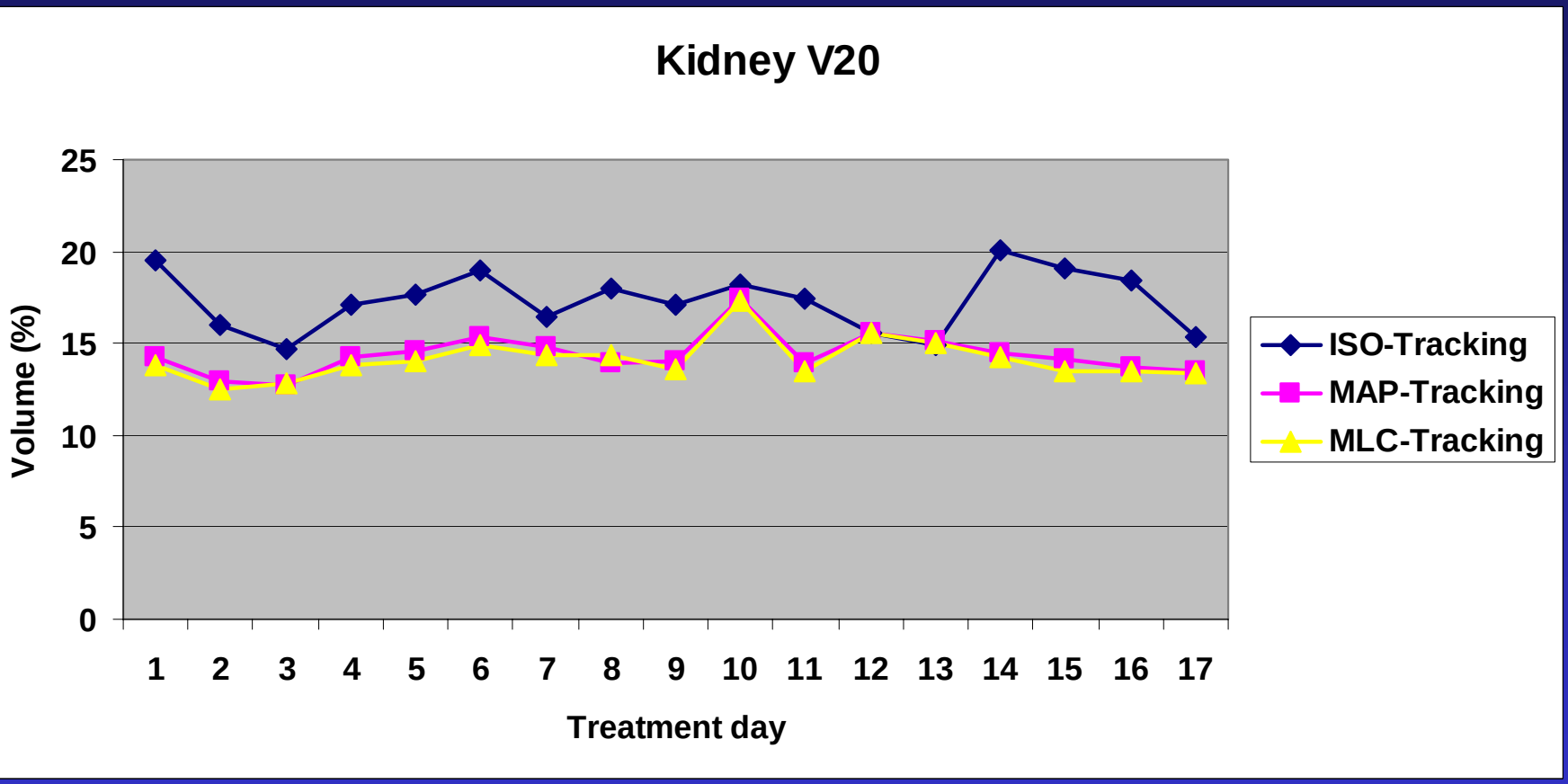

Kidney V20
Volume (%)
25
20
15
10
5
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
Treatment day
ISO-Tracking
MAP-Tracking
MLC-Tracking

Fig. 6c